A temporal transcriptome and methylome in human embryonic stem cell-derived cardiomyocytes identifies novel regulators of early cardiac development.

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Public Summary:
Stem cell-based cardiac tissue generation has become a powerful tool to enhance our understanding of heart development and test novel therapeutics for cardiovascular diseases. However, the transitional stages from pluripotent cells to committed cardiomyocytes has not yet been fully characterized. We utilized a previously reported protocol that yields human cardiomyocytes (hCM) with more than 90% purity from human Embryonic Stem Cells (hESC). Leveraging the purity of cells resulting from this protocol, we systematically examined cardiogenesis, the generation of heart cells. We incorporated a simple but powerful method to screen for novel regulators of cardiogenesis and found four novel candidates. Our strategy of identifying novel regulators of cardiogenesis can also be easily implemented in other stem cell-based systems. Our results provide a valuable resource for understanding cardiogenesis that extends previous findings by leveraging the purity of our cell lines, which allowed us to identify four novel cardiac-related regulators.

Scientific Abstract:
Stem cell-based cardiogenesis has become a powerful tool to enhance our understanding of cardiac development and test novel therapeutics for cardiovascular diseases. However, transcriptional and epigenetic regulation of multiple transitional stages from pluripotent cells to committed cardiomyocytes has not yet been fully characterized. To characterize how transcription factors, lincRNAs and DNA methylation change at temporal developmental stages, and identify potential novel regulators during cardiogenesis. We utilized a previously reported protocol that yields human cardiomyocytes (hCM) with more than 90% purity from human Embryonic Stem Cells (hESC). Leveraging the purity of cells resulting from this protocol, we systematically examined how gene expression and DNA methylation programs change at temporal developmental stages during cardiogenesis. Our results provide a comprehensive view of expression changes during cardiogenesis that extend previous studies, allowing us to identify key transcription factors as well as lincRNAs that are strongly associated with cardiac differentiation. Moreover, we incorporated a simple but powerful method to screen for novel regulators of cardiogenesis solely based on expression changes and found four novel cardiac-related transcription factors, i.e., SORBS2, MITF, DPF3, and ZNF436, which have no or few prior literature reports and we were able to validate using siRNA. Our strategy of identifying novel regulators of cardiogenesis can also be easily implemented in other stem cell-based systems. Our results provide a valuable resource for understanding cardiogenesis that extends previous findings by leveraging the purity of our cell lines, which allowed us to identify four novel cardiac-related regulators.